

REMARKS/ARGUMENTS

As the Examiner may be aware, this application is the first in the world to describe the specific modification of endogenous genes through a genetic targeting event followed by successful nuclear transfer. This invention was heralded in a full paper in Nature magazine in 2000 (McCreath et al. Nature. 2000 Jun 29;405(6790):1066-9) and widely reported as a breakthrough in nuclear transfer and animal cloning.

Since the filing of this patent application and the publication of the McCreath et al. paper, ovine, porcine and bovine animals with genetically targeted modifications have been produced. Between 2002 and 2004, three independent groups, Immerge Biotherapeutics, Inc. in collaboration with the University of Missouri¹, Alexion Pharmaceuticals² and Revivicor, Inc. (formerly PPL Therapeutics, Inc., owner of the pending application)³ produced pigs that lacked one allele or both alleles of the alpha-1,3-GT gene via nuclear transfer from somatic cells with targeted genetic deletions. In 2003, Sedai et al⁴ reported the targeted disruption of one allele of the alpha-1,3-GT gene in cattle, followed by the successful nuclear transfer of the nucleus of the genetically modified cell and production of transgenic fetuses. In 2004, researchers at Hematech, LLC and Kirin Brewery Company, Ltd, reported the production of cows by cloning using somatic cells, which had been specifically modified through genetic targeting. The genome of these somatic cells contained targeted disruptions that inactivated both copies of the immunoglobulin "mu" gene or both copies of the gene encoding the bovine prion protein.⁵ Thus, to date, subsequent to the fundamental teachings of the present application, gene targeting in somatic cells followed by transfer of the genetically modified nucleus into oocytes to produce viable offspring has been accomplished by at least six independent groups in three different animal species to target four different genes. This demonstrates that the invention as broadly described in the application is a successful general approach to achieve genetically modified cloned animals.

¹ Lai et al. (Science (2002) 295: 1089-1092) & Kolber-Simonds et al. (PNAS. (2004) 101(19):7335-40)

² Ramsoondar et al. (Biol Reprod (2003)69: 437-445)

³ Dai et al. (Nature Biotechnology (2002) 20: 251-255) & Phelps et al. (Science (2003) Jan 17;299(5605):411-4)

⁴ Sendai et al. (Transplantation (2003) 76:900-902)

⁵ Kuroiwa et al. (Nat Genet. 2004 Jun 6 Epub)

Claim Rejections - 35 U.S.C § 112

The Examiner has rejected the currently pending claims for lack of enablement under 35 U.S.C. § 112, first paragraph. Specifically, in the current Office Action, the Examiner repeatedly rejects various elements of the claims as non-enabled based on the assertion that the Applicants only describe one way to carry out that particular aspect of the claim. In fact, the reader need only be taught one method to carry out the claimed subject matter. As the Federal Circuit has held:

[t]he purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and knowledge in the art.

Scripps Clinic & Research Foundation v. Genentech, Inc., 18 USPQ2d 1001, 1006 (Fed. Cir. 1991)

The facts surrounding this application are similar to those presented in *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. (TKT)* (314 F.3d 1313 (Fed Cir 2003), copy attached), herein referred to as the “Amgen case”. This Federal Circuit case is binding precedent on the U.S.P.T.O.

Amgen alleged that Hoechst Marion Roussel and TKT infringed various Amgen U.S. patents (U.S. Patent Nos. 5,547,933; 5,618,698; 5,621,080; 5,756,349 and 5,955,422) that covered the production of erythropoietin (“EPO”, a naturally occurring hormone that controls the formation of red blood cells in bone marrow). Exemplary claim 1 of U.S. Patent No. 5,955,422, reads, “A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.”

In the specification, Amgen described one method to produce EPO by cloning the EPO DNA sequence and then expressing the encoded polypeptide in a suitable host cell, i.e., Amgen inserted a heterologous gene encoding EPO into a CHO (Chinese hamster ovary) cell and the cell expressed this heterologous gene (through “heterologous recombination”). TKT denied that it infringed the patents because, in part, Amgen had not enabled the method of genetic modification that TKT used to achieve the production of EPO. TKT’s method to express EPO involved inserting a regulatory sequence of DNA into a cell to ‘switch on’ an endogenous ‘natural’ gene to allow the cell to produce large amounts of the endogenous EPO protein

(through “homologous recombination”). This method did not exist at the priority date of the Amgen patent and was only developed a number of years later. TKT thus argued that its process of producing EPO substantially differed from the method described in Amgen’s patents, which, according to TKT, required a heterologous, or non-native, EPO-encoding sequence. TKT argued that Amgen’s compound and composition claims were overbroad under § 112 and lacked enablement because the specification failed to describe how to produce EPO using human cells or endogenous human EPO DNA, i.e., that Amgen’s claims were not enabled over their full scope. Further, they argued that Amgen should not be entitled to patent protection covering inventions it did not make.

Thus, the question before the CAFC was whether Amgen was entitled to the full scope of the composition claims although the full scope was not enabled. The CAFC disagreed with TKT and provided clarity to the enablement requirement in the biotech area:

Our precedent is clear that claims are not perforce limited to the embodiments disclosed in the specification. E.g., *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1344, 60 USPQ2d 1851, 1856 (Fed. Cir. 2001) (“[A]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention.”)

The enablement requirement is often more indulgent than the written description requirement. The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without “undue experimentation.” *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed.Cir.1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed.Cir.1991).

As to TKT’s endogenous/exogenous arguments, the court concluded the arguments were inapplicable as a matter of law for two reasons. First, “where the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed.” *Amgen*, 126 F.Supp.2d at 160, 57 USPQ2d at 1515 (citing *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465; *In re Koller*, 613 F.2d at 824–25, 204 USPQ at 707; *In re Hogan*, 559 F.2d at 606, 194 USPQ at 538); *see also id.* at 161, 57 USPQ2d at 1516 (discussing the 8080 patent), at 163–64, 57 USPQ2d at 1518 (discussing the 8349 patent). Thus, the specification’s failure to disclose the later-developed endogenous activation technology cannot invalidate the patent. *Id.* at 160, 57 USPQ2d at 1516. Second, **“the law makes clear that the specification need teach only one mode of making and using a claimed composition.”** *Id.* at

160, 57 USPQ2d at 1515 (citing *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1719 (Fed.Cir. 1998); *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed.Cir.1991)); *see also Durel Corp. v. Osram Sylvania Inc.*, 256 F.3d 1298, 1308, 59 USPQ2d 1238, 1244 (Fed.Cir.2001). This conclusion again makes the specification's failure to disclose TKT's endogenous activation technology legally irrelevant. *Amgen*, 126 F.Supp.2d at 160, 57 USPQ2d at 1515.

Emphasis added.

Thus, the CAFC confirmed that Amgen's broad claims to the genetically modified cells and compositions satisfied the enablement requirement under § 112:

Focusing specifically on the '422 patent, the enablement inquiry is whether Amgen has enabled all pharmaceutical compositions comprising "a therapeutically effective amount of human erythropoietin," "a pharmaceutically acceptable diluent, adjuvant or carrier," and human erythropoietin "purified from mammalian cells grown in culture." The court found that the specification described and enabled various possible diluents and carriers and provided specific information on effective dosages and therapeutic effect in mice. *Id.* at 148, 57 USPQ2d at 1506. Amgen also described and enabled at least one way of obtaining EPO purified from mammalian cells in culture: the genetic manipulation of CHO and COS-1 cells, followed by both described and other well known purification techniques. Finally, the court accepted testimony indicating that an ordinarily skilled artisan would infer from the COS-1 (monkey) and CHO cell examples that similar outcomes could be expected from other mammalian cells since all mammalian cells produce and secrete hormones like EPO by means of the same fundamental processes. *Id.* at 159, 57 USPQ2d at 1514-15.

The Examiner's § 112 rejections in the current case do not follow the reasoning behind *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*

The pending claims of the invention are directed to methods for producing a transgenic animal by modifying the nuclear genome of a somatic cell at an endogenous locus by a genetic targeting event and accomplishing successful nuclear transfer. The inventors determined that gene targeting could be achieved in somatic cells and that the nucleus of these cells could be transferred to an oocyte to successfully produce a viable offspring.

In the remarks that follow, the Applicants provide the Examiner with evidence that at least one way to carry out the techniques encompassed by the claims is provided in the specification. Although we have no burden to prove more than one method to carry out the

claimed invention, Applicants also provide the Examiner below with examples of various other methods that were known to one skilled in the art as of April 9, 1999 (the priority date) to accomplish the methods of the present invention. Thus, one skilled in the art would clearly be able to carry out the methods claimed without "undue experimentation" within the interpretation and guidance given by the CAFC in the Amgen case.

(i) Donor cells

The Examiner has rejected claims 62-90 under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The Examiner states that "the art at the time of filing clearly recognized that some outside event to the donor cell in an nuclear transfer procedure must occur for successful development of an nuclear transfer unit" and that "both reprogramming and nuclear/nucleoli remodeling are events that the art regards as necessary for a cell to be completely totipotent, *i.e.*, for the cell to become competent to give rise to a live animal" (citing to Fulka *et al.*, Kono *et al.* and Wolf *et al.*). The Examiner also points out that the specification discusses serum starvation as a means for reprogramming the donor somatic cell nucleus. However, the Examiner asserts that without further guidance as to other means for reprogramming donor cell nuclei, the claims are not enabled for their full breadth.

Applicants note that the Examiner had previously rejected similar claims of the parent case, 09/475,674, as non-enabled on the same basis in an Office Action dated July 18, 2000 (copy attached). Applicants responded to this rejection on February 23, 2001 (copy attached) subsequent to the filing of a Continued Prosecution Application on January 18, 2001. Applicants believed that the Examiner's rejections had been successfully overcome as evidenced by the fact that this rejection was not maintained in the two subsequent Office Actions issued in the parent case.

Applicants have the burden of establishing only that they provided one clear method of enablement for the claim term at issue. Applicants have done this, as the Examiner correctly noted. In the Example section, on page 51, lines 2-5, of the specification, Applicants teach the public how to use serum starvation to create G₀ donor cells.

In addition to serum starvation, other methods of accomplishing this reprogramming, such as chemical treatments, growth inhibition or manipulation of gene expression, were well-

known in the art at the time of filing of the present application. The Specification itself cites to several references that teach methods of reprogramming donor cells, for example:

(i) WO 97/07668 to the Roslin Institute, which was cited on page 1, lines 21-23, teaches the use of cells in the G0 or G1 phase of the cell cycle that contain diploid nuclei as donor cells;

(ii) WO 98/39416 to Infigen, Inc., which was cited on page 1, lines 25-27, teaches the reprogramming of non-totipotent cells to totipotent cells that are used as nuclear donors through incubation in a receptor ligand cocktail;

(iii) WO 98/30683, WO 98/07841 and WO 99/01164 to the University of Massachusetts, which were cited on page 1, lines 25-27, teach the use of a differentiated fetal and adult cells as donor cells; and

(iv) WO 99/01163 to the University of Massachusetts, which was cited on page 1, lines 25-27, teaches the use of non-serum starved, differentiated cells as donor cells.

In addition, contact inhibited donor cells (Kato et al (2000) 120: 231-237); roscovitine-pretreated donor cells (Gibbons et al (2002) Biol Reprod 66: 895-900); and metaphase-stage synchronized donor cells (Ono et al (2001) Reproduction 122: 731-736) are also known to those of skill in the art.

Therefore, Applicants believe that claims 62-90 are fully enabled to allow one skilled in the art to reprogram the nucleus of a donor cell.

(ii) Somatic Cells

The Examiner has rejected claims 62-90 under 35 U.S.C. 112, first paragraph on the basis that the claims recite methods of modifying the nuclear genome of a somatic cell at an endogenous locus by a genetic targeting event, and that the breadth of the claims encompasses utilizing any somatic cell. The Examiner contends that due to the unpredictability in the art of gene targeting of somatic cells (citing to Thomson *et al.* (Reprod. Supp., 61:495-508 (2003)) and Polejaeva and Campbell (Theriogenology, 53:117-126 (2000))). Applicants have established that one can use primary ovine fetal fibroblasts [Examples 1-4], primary mammary epithelial cells [Example 5], porcine fetal fibroblasts [Example 6] and primary bovine fetal fibroblasts [Example 7]. Contrary to the Examiner's suggestion, therefore, the present invention provides working examples using cells from three different species, i.e. ovine, porcine and bovine, and

two very different cells types, i.e. fibroblasts and epithelial cells, which clearly establishes the breadth of the method.

Further, the Examiner states that Thomson teaches that premature senescence often occurs, which makes it difficult to confirm a targeting event in somatic cells and that cloning efficiency has been negatively correlated with passage number. This factor is commonly known in the art as the "Hayflick limit" (Hayflick Exp Cell Res. 1965 Mar;37:614-36) and is routinely taken into account and overcome by scientists skilled in the cloning art. The Hayflick limit is not a barrier to cloning, but merely a realization that in every cell population, some percentage of cells will die prematurely. This is an issue that is true for any cell type and is a routine consideration in experimental design by those skilled in the art.

The Examiner also cites to Polejaeva and Campbell who teach that there is a lower frequency of homologous recombination in somatic cells than ES cells, and that there is a finite number of cell divisions for somatic cells. Thus, Polejaeva and Campbell teach that homologous recombination will occur in somatic cells at a low frequency. Applicants note that there is no burden on the patentee to teach only highly efficient techniques to accomplish the invention. The patent must teach at least one mode to carry out the invention. Indeed, the present invention provides the fundamental advance, despite prior assumptions to the contrary, that homologous recombination in somatic cells and the nuclear transfer process can be successfully combined.

Further, the Examiner points out that Polejaeva and Campbell note that human dermal fibroblasts are not able to proliferate under regular culture conditions, and thus, optimization of culture conditions must be attained for success in somatic cell gene targeting. This point is rendered moot since the present claims have been amended to recite methods to produce non-human transgenic animals.

(iii) Oocytes

The Examiner asserts that the pending claims are overbroad on the basis that the claims encompass methods of nuclear transfer utilizing any mammalian oocyte. The Examiner cites to Campbell et al. (Cloning & Stem Cells, 3(4):201-208 (2001)) and Fulka et al. (Theriogenology, 55(6):1373-1380 (2001)) to conclude that the state of the art supports that only oocytes in MII or oocytes in telophase II be used for successful nuclear transfer. Applicants note that the claims recite methods of nuclear transfer utilizing recipient cells, which include, but are not limited to,

oocytes. Other types of recipient cells can also be used, such as zygotes and two cell embryos (see, for example, page 16, lines 11-26).

Applicants also note that the claimed invention does not rely on any special method of nuclear transfer. The present invention is NOT directed to nuclear transfer and does not provide any advance in the nuclear transfer art per se. The invention is the fundamental achievement of the combination of gene targeting and nuclear transfer. Therefore, as stated on page 8, line 29; and at page 9, line 9 of the specification "any method of nuclear transfer may be used in accordance with the methods of the presently claimed invention".

The Examiner correctly states that presently at least three types of oocytes are available to those of skill in the art, as described by Fulka et al. In fact, other types of oocytes can be used, see for example, Miyoshi et al. (BMC Developmental Biology (2001) 1:12), which teaches the use of metaphase I stage oocytes and Baguisi et al. (Nature Biotech (1999) 17:456), which teaches the use of telophase II stage oocytes for nuclear transfer. Additionally, other types of oocytes may be discovered in the future. Since the Applicants' invention is not nuclear transfer, we should not be limited to a specific method that the public can use to produce the genetically modified animal wherein the gene is modified by a genetic targeting event. Similarly, as described above in the Amgen case, the CAFC noted that "[A]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention."

The specification teaches nuclear transfer to an oocyte. The type of oocyte is not relevant. Any oocyte that can be used for nuclear transfer, which is known to one skilled in the art of cloning, can be used. As the Examiner correctly notes, the specification does provide for the use of a metaphase II oocyte on page 16, lines 11-26, thus the Applicants burden to provide at least one way to carry out the method of the present invention is fulfilled.

(iv) Activation

The Examiner has rejected the currently pending claims for failing to provide a step of activating the nuclear transfer unit. Applicants have amended independent claims 62 and 90 to include an activation step and new independent claims 132 and 133 include an activation step, which, as the Examiner points out, is supported on page 18, lines 12-25 of the specification.

Alternatively, new independent claim 131 requires successful nuclear transfer which would inherently require an activation step.

(v) Surrogate mother

The Examiner has rejected the currently pending claims for failing to provide a step of transferring the resulting nuclear transfer unit into a surrogate mother. Applicants have amended the claims to include this step. As the Examiner points out, the specification supports the step of transferring the resulting nuclear transfer unit into a surrogate mother on page 19, lines 2-4.

In addition, the Examiner rejects the pending claims for lack of enablement because they do not provide a step of transferring the resulting embryo into a surrogate mother of the same species. Whether or not a surrogate mother can carry an embryo of another species to term is an inherent limitation known to those skilled in the art. There are indeed various combinations of species that can successfully carry an embryo of another species, for example:

- (i) Alpacas have been gestated in the womb of llamas;
- (ii) African wildcat (*Felis silvestris libyca*) embryos have been gestated in the womb of a domestic cat (*Felis catus*);
- (iii) Przewalski's horse (*Equus przewalskii*) and Grant's zebra embryos have been gestated in the womb of domestic mares (*Equus caballus*) (Summers et al J Reprod Fertil. 1987 May;80(1):13-20);
- (iv) Horse (*Equus caballus*) embryos have been gestated in the womb of a Jack donkey (*Equus asinus*) (Camillo et al. Reprod Domest Anim. 2003 Oct;38(5):380-5); and
- (v) European mink (*Mustela lutreola*) embryos have been gestated in the womb of a hybrid mink (cross between *Mustela lutreola* and *Mustela putorius*) (Amstislavsky et al Theriogenology. 2004 Aug;62(3-4):458-67).

In addition, the successful cloning of one species that is gestated in the womb of another species has been accomplished. For example, in 2000, Lanza et al. (Cloning, 2(2):79-90, 2000) reported the birth of a cloned bull guar, which represented the first individual of an endangered species to be cloned and then brought successfully to term by a surrogate mother from another, more common, species, in this case a domestic cow. In 2001, Loi et al. (Nature Biotech (2001) 19:962) reported the successful cloning of a wild endangered animal, the mouflon (*Ovis orientalis musimon*), which was gestated in the womb of a sheep (*Ovis aries*). As stated above,

as affirmed by the CAFC in the Amgen case, future developments in the art can be encompassed by the claims of an earlier filed patent application, thus the Applicants should not be limited to claims wherein the animal cloned is gestated in the womb of an animal of the same species.

(vi) Cloning humans

The Examiner has rejected the currently pending claims because the breadth of the claimed invention encompasses cloning humans. Applicants have amended the claims to recite “a method for producing a non-human transgenic animal”.

(vii) Abundantly expressed locus

The Examiner has rejected claims 67, 68 and 74, which state that the genetic targeting event result in the a gene targeted cell clone randomly targeted cell clone ratio of equal or greater than 1:100 or that the gene targeting even is carried out at a locus abundantly expressed in the somatic cell. Claims 67, 68 and 74 have been canceled without prejudice. Applicants reserve the right to pursue these claims in a separate application.

(viii) Transgenic animals

The Examiner has rejected the currently pending claims for failing to provide an appropriate phenotype for the resulting animal because the state of the art of generating transgenic animals is unpredictable with regard to the resulting phenotype. This application concerns genotypic, not phenotypic, changes. Applicants note that there is no requirement in the claims that the genetic modification result in an altered phenotype in the transgenic animal produced. The pending claims are directed to methods to produce animals that bear a transgene at a specified location within the genome of that animal. Further, to date, three different types of animals (sheep, cows and pigs) with four different types of targeted genetically modifications have been produced through cloning by six independent groups.

Claim Rejections - 35 U.S.C §112

The Examiner rejected claims 62 and 90 under § 112, second paragraph for failing to point out and distinctly claim the subject matter. Claims 62 and 90 have been amended to

include the specific method steps that the Examiner suggested. Amended claim 62 and 90 now contain the additional steps of “activating the nuclear transfer unit thereby producing an animal embryo” and “transferring the embryo to a surrogate mother”, which is then followed by the subsequent development of the embryo to term.

The Examiner has also rejected the term “abundantly” in claims 68 and 74. Claims 68 and 74 have been canceled.

Claim Rejections - 35 U.S.C §103

The Examiner has rejected pending claims 62-75, 82-87 and 90 under 35 U.S.C. 103(a) as unpatentable over Schnieke *et al.* (*Science* 278:2130-2133 (1997)) in view of Stacey *et al.* (*Molec. Cell. Biol.* 14:1009-1016 (1994), herein referred to as Stacey I) and Stacey *et al.* (*Proc. Natl. Acad. Sci. USA* 92:2835-2839 (1995), herein referred to as Stacey II). Applicants note that the Examiner had previously rejected similar claims of the parent case, 09/475,674, as obvious in view of the same art in an Office Action dated July 18, 2000 (copy attached). Applicants responded to this rejection on February 23, 2001 (copy attached) subsequent to the filing of a Continued Prosecution Application on January 18, 2001. Applicants believed that the Examiner’s rejections had been successfully overcome as evidenced by the fact that this rejection was not maintained in the two subsequent Office Actions issued in the parent case.

The invention as presently claimed is drawn to methods of preparing somatic cells for nuclear transfer comprising modifying the genetic material of the somatic cell at an endogenous (*i.e.*, a naturally occurring) locus by a genetic targeting event. As the Examiner has acknowledged, Schnieke does not disclose such methods, particularly methods wherein the genetic material of the somatic cell is engineered at a precise endogenous genetic locus. Hence, Schnieke is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of Schnieke are not cured by the disclosures of Stacey I and Stacey II. First, applicants note that both Stacey I and Stacey II disclose genetic modification (specifically, in the α -lactalbumin gene rather than in the β -lactoglobulin gene (which is not present in mouse)) of mouse ES cells. Contrary to the Examiner’s contention in the January 18, 2001 Office Action at page 11, lines 17-18, and as the ordinarily skilled artisan would appreciate, ES cells are *not* somatic cells. As the specification of the present application states:

(t)raditionally, cells can be defined as either “somatic”, or “germ-line”. Some cells, e.g. ES cells may not fall easily in either of these two traditional categories because they are derived from embryos *before distinct somatic and germ lineages can be distinguished*. Their functional equivalent, EG (Embryonic germ) cells are more easily defined as “germ-line” cells because they are derived from primordial germ cells. *In the present text, the term “somatic” does not cover ES or EG cells.*

Specification at page 5, lines 3-9. Thus, one of ordinary skill reading Schnieke in view of either Stacey I or Stacey II could have obtained no guidance that would have permitted the production and use of *somatic* cells prepared for nuclear transfer by the presently claimed methods.

Second, there is no specific suggestion or motivation that would lead one of ordinary skill to have combined the disclosures of Stacey I and/or Stacey II in order to produce the presently claimed invention. Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Thus, the Examiner has not met the burden required to sustain a *prima facie* case of obviousness.

Finally, even if these references could be properly combined (which they cannot) and disclosed all of the elements of the presently claimed invention (which they do not), the present invention provides at least one secondary indication of nonobviousness over such a theoretical combined disclosure of the cited art -- unexpected results -- which has long been recognized as a classical secondary indication of nonobviousness. *See Graham v. John Deere Co.*, 86 S.Ct. 684, 694 (1966); *Custom Accessories v. Jeffrey-Allan Industries*, 807 F.2d 955, 960 (Fed. Cir. 1986); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Specifically, the present application provides surprising and unexpected results relative to those available in the art at the time of filing of the present application. For example, the present application demonstrates for the first time that, contrary to previous teachings, a primary somatic cell can be modified *in vitro* by gene targeting and can subsequently support successful nuclear transfer to produce a healthy animal. Reasons why this would have been a surprising (*i.e.*, a nonobvious) finding include: Targeting in primary cells, as opposed to immortalized cells, was *previously thought to be impractical* because the expected low frequency of homologous recombination meant that it would be necessary to

transfect and screen large cell populations.⁶ This process requires the cells to maintain a normal cell type during a period of cell culture long enough to allow for identification of targeted cell clones. However, the high frequency of homologous recombination actually achieved minimized the time in culture, allowing the cells to remain viable for sufficient time to allow selection of targeted clones for successful nuclear transfer. Frequency of successful targeting in somatic cells was previously thought to be significantly lower than in ES cells.⁷ Genetic manipulation may disrupt the necessary mechanism which allows a donor nucleus to develop into a healthy animal. The ultimate production of live animals (as shown in the Examples in the present application) is a stringent test for donor cell normality, and success could not have been said to be obvious or expected.

One of ordinary skill therefore would have had no reason to predict that the nuclear genome of a somatic cell could be modified at an endogenous locus by a genetic targeting event and that the nucleus of the genetically modified somatic cell could be used to accomplish successful nuclear transfer, prior to the work of the present inventors. Thus, it is clear that the present invention provides results that were not expected in view of knowledge available in the art as of the filing date of the present application, which the Federal Circuit has recognized as “[o]ne way for a patent applicant to rebut a *prima facie* case of obviousness . . .” *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Moreover, such results were unexpected compared with the closest prior art cited by the Examiner (*i.e.*, Schnieke, Stacey I and Stacey II), which is the standard for judging unexpected results in an obviousness context. *See In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984); *see also In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Therefore, this classical secondary indicator of nonobviousness -- unexpected results -- falls in favor of the presently claimed invention. Hence, under *Graham, Custom Accessories*

⁶ *See, e.g.*, Finn *et al.*, *Molec. Cell. Biol.* 9:4009-4017 (1989) (Doc. No. AT17 on the Supplemental Information Disclosure Statement (“IDS”) filed with the 2/23/01 response) (which shows that the frequency of homologous recombination (“HR”) is substantially higher in an immortal cell line than in the diploid normal cell line from which it was derived); Thyagarajan *et al.*, *Nucl. Acids Res.* 24:4084-4091 (1996) (Doc. No. AS19 on the IDS filed with the 2/23/01 response) (which compares HR levels in a number of immortalized and primary cell lines, and clearly shows that HR frequency in immortalized cells is around 100 times higher than in normal primary cells).

⁷ *See, e.g.*, Hanson *et al.*, *Molec. Cell. Biol.* 15:45-51 (1995) (Doc. No. ARI8 on the IDS filed with the 2/23/01 response) (which states, at page 45, middle of paragraph 2, that “[e]vidence is accumulating that gene targeting in embryonic stem (ES) cells is significantly more efficient than in other cell types.”); and Porter *et al.*, *Transplantation* 64:1227-1235 (1997) (Doc. No. AS18 on the IDS filed with the 2/23/01 response) (in which the entire paragraph on gene targeting in somatic cells at page 1229 points to the fact that targeting in somatic cells is problematic and major improvements are required both in the manipulation of somatic cells in culture and in the efficiency of gene targeting itself; Applicants contend that such improvements are provided by the presently claimed invention).

and *Soni*, the invention as presently claimed would not have been considered to have been obvious.

Thus, there was no expectation that Schnieke could have been modified by the use of genetic targeting, such as that described in Stacey I or Stacey II, to arrive at the methods now claimed with any reasonable expectation of success. In addition, the invention as presently claimed is based upon unexpected results. Therefore, the presently claimed invention would not have been obvious over Schnieke, Stacey I and Stacey II, alone or in combination.

In view of the foregoing remarks, Applicants respectfully assert that the rejection under 35 U.S.C. § 103(a) over Schnieke, Stacey I and Stacey II that was made in the previous Office Action should not be maintained.

Priority

The Examiner correctly remarks that this application is a continuation of U.S. Patent Application No. 09/475,674, as noted in the Preliminary Amendment filed February 25, 2002, which directed that reference to prior applications be entered in the first sentence of the specification:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 09/475,674, filed December 30, 1999, which claims the benefit of U.S. Provisional Application No. 60/128,544, filed April 9, 1999. This application also claims priority to Great Britain Patent Application No. 9905033.8, filed March 4, 1999, and to Great Britain Patent Application No. 9907023.5, filed July 20, 1999. The contents of the foregoing U.S. and Great Britain patent applications are hereby incorporated by reference in their entireties.


The Examiner acknowledged Applicants claim for foreign priority based on an application filed in the United Kingdom on 3/4/99 [9905033.8] and 7/20/99 [9917023.5], but, that the applicant has not filed a certified copy of the two U.K. applications as required by 35 U.S.C. 119(b). Applicants are in the process of obtaining the certified priority documents and will transmit them to the U.S.P.T.O. as soon as they are received.

It is respectfully believed that this application is in condition for allowance. Early action is respectfully requested. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

No fees are believed to be due in connection with this response. However, should the Commissioner determine otherwise, he is authorized to charge such fees and credit any overpayment to Deposit Account No. 11-0980.

Respectfully submitted,

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